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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/992,235	LEDERMAN ET AL.	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 September 2008 and 11 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 25-31* is/are pending in the application.

4a) Of the above claim(s) *25-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 28-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-8 and 25-31 are presented for examination.

Applicant's Amendment filed September 9, 2008 and the duplicate amendment filed September 11, 2008 have each been received and entered into the present application.

Claims 1-8 and 25-31 are pending. Claims 25-31 are newly added. No claims have been cancelled or amended.

Applicant's arguments and amendments, filed September 9, 2008 and September 11, 2008, have been fully considered. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

Withdrawal of Newly Added Claims 25-27: Election by Original Presentation

Applicant's amendment to add new claims 25-31 has been carefully considered in light of the subject matter that was elected and examined in the previous non-final Office Action.

The MPEP states at §819:

"The general policy of the Office is not to permit the Applicant to shift to claiming another invention after an election is once made and action given on the elected subject matter."

Newly submitted claims 25-27 are directed to a patentably distinct invention from the invention originally claimed for the following reason: newly added claims 25-27 are directed to a method for preparing (R,R'),(R,S')-amphetaminil substantially free of (S,R'),(S,S')-amphetaminil, whereas the claims as originally under examination were directed to a pharmaceutical composition comprising an effective amount of (R,R'),(R,S')-amphetaminil sulfate or another pharmaceutically acceptable salt thereof substantially free of (S,R'),(S,S')-amphetaminil.

The inventions are distinct because they are related as process of making and product made, which can be shown to be distinct if: (1) that the process as claimed can be used to make another and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case, newly added claims 25-27 are directed to a process of preparing the claimed composition comprising (R,R'),(R,S')-amphetaminil substantially free of (S,R'),(S,S')-amphetaminil, which can be produced by the method described by Salvesen et al. (already of record, see p.137) in combination with high pressure liquid chromatography.

Since Applicant has received an action on the merits for the originally presented invention directed to a pharmaceutical composition comprising an effective amount of (R,R'),(R,S')-amphetaminil sulfate or another pharmaceutically acceptable salt thereof substantially free of (S,R'),(S,S')-amphetaminil, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 25-27 are withdrawn from consideration as being directed to a non-elected invention. Please see 37 C.F.R. 1.142(b) and MPEP §821.03. As stated in the MPEP at §818.02(a), "The claims originally presented and acted upon by the Office on their merits determine the invention elected by an Applicant in the application, and in any request for continued examination (RCE) which has been filed for the application. Subsequently presented claims to an invention other than that acted upon should be treated as provided in MPEP §821.03."

Claim Rejections - 35 USC § 112, First Paragraph, Scope of Enablement Requirement

(New Grounds of Rejection)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 30-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of a disorder benefiting from or requiring a central nervous system stimulant (i.e., narcolepsy, attention deficit hyperactivity disorder, depression, Parkinson's disease, cognitive dysfunction, Alzheimer's disease, renal dysfunction, asthma, obesity, nicotine withdrawal, hypotension, apathy, potentiating an opiate for pain control and reduced energy associated with chemotherapy or radiation therapy, as in instant claim 31) using the claimed pharmaceutical composition, does not reasonably provide enablement for the prevention of the same using the claimed pharmaceutical composition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1) the nature of the invention;
2) the breadth of the claims;
3) the predictability or unpredictability of the art;
4) the amount of direction or guidance presented;
5) the presence or absence of working examples;
6) the quantity of experimentation necessary;
7) the state of the prior art; and,
8) the relative skill of those skilled in the art.

The relevant factors are addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

For the purposes of consideration under 35 U.S.C. 112, first paragraph, the instant rejection focuses on the particular condition of Alzheimer's disease, as recited in present claim 31. However, the reasons stated here concerning the burden of enabling the prevention of the condition of Alzheimer's

disease apply also to the myriad of other conditions encompassed by the present claims, but for the obvious difference in the type of disorder.

The present invention is directed to a pharmaceutical composition comprising an effective amount of (R,R'), (R,S')-amphetaminil sulfate or another pharmaceutically acceptable salt thereof for the treatment or prevention of a disorder benefiting from or requiring a central nervous stimulant, substantially free of (S,R'),(S,S')-amphetaminil, and at least one pharmaceutically acceptable carrier, diluent, excipient or additive. Instant claim 31 further defines the disorders that may be treated as including narcolepsy, attention deficit hyperactivity disorder, depression, Parkinson's disease, cognitive dysfunction, Alzheimer's disease, renal dysfunction, asthma, obesity, nicotine withdrawal, hypotension, apathy, potentiating an opiate for pain control, and reduced energy associated with chemotherapy or radiation therapy.

In particular, one skilled in the art could not practice the presently claimed subject matter of preventing Alzheimer's disease by administering the claimed amphetaminil composition without undue experimentation because the artisan would not accept on its face that prevention of Alzheimer's disease could actually be achieved given the state of the art at the time of the invention. Based upon the state of the art, as discussed below, and the evidence presented by Applicant, the artisan would have only accepted that the condition could be treated with this amphetaminil composition as instantly claimed.

As set forth in *In re Marzocchi et al.*, 169 USPQ 367 (CCPA 1971):

"[A] [s]pecification disclosure which contains the teachings of manner and process of making and using the invention in terms corresponding to the scope to those used in describing and defining subject matter sought to be patented must be taken as in compliance with the enabling requirement of first paragraph of 35 U.S.C. 112, *unless there is reason to doubt the objective truth of statements contained therein which must be relied on for enabling support;* assuming that sufficient reasons for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis, such a rejection

can be overcome by suitable proofs indicating that teaching contained in the specification is truly enabling." (emphasis added)

The present claims circumscribe the use of the presently claimed amphetaminil composition for the prevention of Alzheimer's disease. That is, in order to be enabled to practice the present invention, the skilled artisan would have to accept that by using a pharmaceutical composition comprising the presently claimed amphetaminil compound that Alzheimer's disease would actually be prevented from developing or worsening or that the onset of Alzheimer's disease could be prevented. In other words, the skilled artisan would have understood the term "prevention" to mean that the claimed composition was capable of impeding the development of such a condition such that it would be "prevented", i.e., reasonably expected not to occur, in such a population treated via the instantly claimed composition. Because such preventive success is not reasonably possible with most diseases or disorders, especially a condition as complex and poorly understood as Alzheimer's disease, the specification, which lacks any direction or guidance as to how prevention of Alzheimer's disease could actually be achieved, is viewed as lacking an enabling disclosure of the entire scope of the claimed invention.

Regarding the prevention of Alzheimer's disease, the objective truth of the statement that Alzheimer's disease may be prevented or can be delayed from developing is doubted because the disease is particularly elusive and manifests itself in a variety of different ways in different subjects such that the diagnostician cannot be sure that the disease is truly the cause of the signs and symptoms of disorder exhibited by the patient. A diagnosis of Alzheimer's disease is tentative, at best, until confirmation of the diagnosis can be confirmed by the presence of amyloid deposits in the brain at autopsy (see Cecil's Textbook of Medicine, "Differential Diagnosis", page 2043 at column 1).

Such difficulties in diagnosis are recognized in the art. Applicant's attention is drawn to Cecil's Textbook of Medicine, which states, "In a patient with clinical findings suggesting Alzheimer's disease, other causes of dementia should be excluded by history, examination, and the laboratory studies described

above. CSF evaluation for amyloid protein and tau protein can increase the likelihood of a diagnosis of Alzheimer's disease, but they are not sufficiently specific to be of routine value in screening or early diagnosis of Alzheimer's disease…Presence of the apoE4 allele makes it very likely that the patient's dementia is produced by Alzheimer's disease. ApoE testing does not have predictive value for asymptomatic individuals." (see Cecil's Textbook of Medicine, "Diagnosis", column 2 at page 2044)

In this regard, it is also noted that the art acknowledges only certain criteria for definitive diagnosis of Alzheimer's disease, see in particular Gauthier et al., (Can. Med. Assoc. J, Oct 15, 1997, 157(8): 1047-52), Greicius et al. (J Neurol. Neurosurg. Psychiatry, 2002 Jun; 72(6):691-700) and Gasparini et al. (FASEB J., 12, Jan. 1998, pp. 17-34). Post mortem analysis of brain tissue for the characteristics of amyloid plaques is considered necessary for a definitive diagnosis. This is because the art has come to recognize its presence in essentially all cases. However, to achieve diagnostic status took years of evaluative procedures, both pre- and post-mortem, confirming that every case had a degree of this pathology. Even so, diagnostic application is often problematic given variable peptide expression patterns among clinically similar and dissimilar diseases states (see Greicius et al.).

Given that there a only a few factors that are recognized to have moderate, if any, predictive value in determining the likelihood that patients develop such a disease or to even determine whether patients actually have such a disease, since many of the early signs of Alzheimer's disease are common complaints of aging or result from other neurological conditions, such as depression, where memory impairment is not present (see Cecil's Textbook of Medicine, "Evaluation of Dementia", column 1, page 2042), one of ordinary skill in the art would not accept on its face Applicant's statement that the onset of Alzheimer's disease could be delayed and/or prevented using the presently claimed composition of amphetaminil. In fact, such complexity of diagnosis precludes a common, art-accepted protocol for preventing or delaying the onset of Alzheimer's disease in any patient, given that the circumstances or risk factors are unique to that individual and must be considered on a case-by-case basis when

determining the most effective approach to delaying or preventing Alzheimer's disease.

In other words, not only is the population in need of such treatment not particularly well defined in the art because of the difficulties associated with making an accurate diagnosis, but the disease is also sufficiently complicated and poorly understood such that the idea that any active agent (including that presently claimed) would be capable of delaying or preventing the onset of such a condition via the use of the presently claimed composition would not have been reasonably expected by the skilled artisan. The artisan would have required sufficient direction as to how the administration of the presently claimed active composition of amphetaminil could actually determine the population of patients in need of prevention and how the presently claimed composition could actually delay or prevent Alzheimer's disease such that the artisan would have been imbued with at least a reasonable expectation of success. Such success would not have been reasonably expected given that the concept of a single agent, or even a combination of agents, that is effective against the development of Alzheimer's disease would have been unique and, thus, met with a great deal of skepticism.

It is in this regard that Applicant is directed to the MPEP at §2164.08. All questions of enablement are evaluated against the claimed subject matter. Concerning the breadth of a claim relevant to enablement, the only relevant concern is whether the scope of enablement provided to one skilled in the art by the disclosure is commensurate with the scope of protection sought by the claims. The determination of the propriety of a rejection based upon the scope of a claim relative to the scope of enablement involved the determination of how broad the claim is with respect to the disclosure and the determination of whether one skilled in the art is enabled to use the *entire scope* of the claimed invention without undue experimentation.

Applicant provides various exemplary methods of synthesis and a study of the instantly claimed amphetaminil isomer in rats assessed for various motor activities. However, none of these studies demonstrates the ability of the claimed amphetaminil composition to effectively delay the onset of or

prevent Alzheimer's disease. While a lack of a working embodiment cannot be the sole factor in determining enablement, the absence of substantial evidence commensurate in scope with the presently claimed subject matter, in light of the unpredictable nature of the art and the direction that Applicant has presented, provides additional weight to the present conclusion of insufficient enablement in consideration of the *Wands* factors as a whole. The instant specification conspicuously lacks any disclosure or teaching of manner and process of using the presently claimed compound for achieving the objective of delaying the onset of or preventing Alzheimer's disease itself. Nowhere does the specification disclose the manner or procedure of using the presently claimed amphetaminil composition for preventing Alzheimer's disease such that the skilled artisan would have been imbued with at least a reasonable expectation of success in determining those patients population in need of prevention of Alzheimer's disease without the burden of an undue level of experimentation.

The basis for the present rejection is not simply that experimentation would be required, since it is clear from the state of the pharmaceutical and chemical arts that experimentation in this particular art is not at all uncommon, but that the level of experimentation required in order to practice this aspect of the invention in the absence of any enabling direction by Applicant would be *undue*. Please reference *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976), which states, "The test of enablement is not whether any experimentation is necessary, but whether, *if experimentation is necessary, it is undue*." (emphasis added)

In view of the discussion of each of the preceding seven factors, the level of skill in the art is high and is at least that of a medical doctor with several years of experience in the art.

As the cited art and discussion of the above factors establish, practicing the claimed method in the manner disclosed by Applicant would not imbue the skilled artisan with a reasonable expectation that the objective of preventing the claimed disorders in a subject using the claimed amphetaminil composition could be achieved. In order to actually achieve such a result, it is clear from the discussion above that the

skilled artisan could not rely upon Applicant's disclosure as required by 35 U.S.C. 112, first paragraph, and would have no alternative recourse but the impermissible burden of undue experimentation in order to practice the full scope of the presently claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8 and 28-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Salvesen et al. ("NMR and ORD Determination of the Configuration of the N-Cyanobenzylamphetamine (AN 1)", *Aezneim-Forsch. (Drug Res.)*, 1974; 24(2):137-140), in light of STN Registry File No. 17590-01-1 ("Amphetaminil", 2008) and Stedman's Medical Dictionary (Twenty-Second Edition, 1972; p.377), each cited to show facts, in view of Remington's Pharmaceutical Sciences (Sixteenth Edition, 1980; p.420-425), each already of record, for the reasons of record set forth at p.2-6 of the previous Office Action dated June 12, 2008, of which said reasons are herein incorporated by reference.

Newly added claims 28-31 are properly included in the instant rejection because Salvesen et al. teaches that the compound N-cyanobenzylamphetamine (also known as AN1; col.1, para.1, p.137) is marketed in dragees with a content of 10 mg α-phenyl-α'-N-(beta-phenylisopropylamino) acetonitrile, which has a general stimulant effect (col.1, para.1, p.137). Salvesen et al. further teaches that the compound can exist in two diastereoisomeric forms (col.1, para.2, p.137) and discloses that synthesis of N-cyanobenzylamphetamine from S-(+)-amphetamine renders a diastereoisomeric mixture of [(αS, α'R),(αS, α'S)] N-cyanobenzylamphetamine and the synthesis of the same from R-(-)-amphetamine renders the diastereoisomeric mixture of [(αR, α'R),(αR, α'S)] N-cyanobenzylamphetamine (col.2, para.4, p.138), thus, supporting the conclusion that four stereoisomers of the compound N-cyanobenzylamphetamine were known and identified in the art (col.2, para.6, p.138). Note that the term N-cyanobenzylamphetamine, or "AN1", and the term "α-phenyl-α'-N-(beta-phenylisopropylamino) acetonitrile" are each synonymous with the term amphetaminil as used in, e.g., instant claim 1, as evidenced by STN Registry File No. 17590-01-1.

Stedman's Medical Dictionary (Twenty-Second Edition, 1972; p.377) is cited to show that dragees are sugar-coated pills or capsules. Accordingly, the very fact that Salvesen et al. teaches a formulation of the disclosed N-cyanobenzylamphetamine compound necessarily requires, though not explicitly stated in Salvesen et al., sugar to coat the pill or capsule to form the dragees. As a result, the inherent presence of sugar in the dragee formulation necessarily meets Applicant's limitation directed to "at least one pharmaceutically acceptable carrier, diluent, excipient or additive" as recited in instant claim 30.

Salvesen et al. fails to teach (1) (R,R'),(R,S')-amphetaminil substantially free of (S,R'),(S,S')-amphetaminil prepared by the method of claim 25 (claim 28), (2) wherein the amphetaminil is the sulfate or other pharmaceutically acceptable salt (claim 29) or (3) a pharmaceutical composition comprising a pharmaceutically acceptable salt of (R,R'),(R,S')-amphetaminil substantially free of a pharmaceutically

acceptable salt of (S,R'),(S,S')-amphetaminil for the treatment or prevention of a disorder benefiting from or requiring a central nervous system stimulant (claims 30-31).

Regarding (1), though it is noted that Salvesen et al. teaches a formulation containing a racemic mixture of the four stereoisomeric configurations of N-cyanobenzylamphetamine (i.e., amphetaminil) and fails to expressly teach (R,R'),(R,S')-amphetaminil substantially free of (S,R'),(S,S')-amphetaminil, one of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to modify the stereoisomeric mixture of the compound N-cyanobenzylamphetamine (i.e., amphetaminil) (col.2, para.6, p.138), as disclosed by Salvesen et al., to contain the isomeric configurations with the greatest activity over the others because isomers of a racemic mixture are reasonably expected to have differing activities such that particular isomers are generally expected to be more active than others due to the fact that living systems are chiral and, thus, preferentially process certain stereochemical configurations over others. In other words, optically active isomer isolation from a racemic mixture would have been *prima facie* obvious to one of skill in the art at the time of the invention due to the reasonable expectation of greater activity from one isomer over the other. Motivation to include isomeric configurations from a disclosed mixture flows logically from the desirability of producing a pharmaceutical composition that will produce an optimal therapeutic effect. Please reference *In re Anthony*, 162 USPQ 594, and *In re Adamson*, 125 USPQ 233. Moreover, in consideration of the fact that the skilled artisan would have been reasonably apprised of conventional methods of isolation and purification, such as various chromatographic methods, the artisan would have predictably used such methods within the knowledge and possession of one of ordinary skill in the art to isolate and concentrate the desired isomeric configuration to meet the instantly claimed requirement of being "substantially free" of the (S,R'),(S,S')-amphetaminil.

Further, though it is noted that Salvesen et al. does not explicitly teach the instantly claimed method of preparation as recited in instant claim 25 (i.e., obtaining racemic material and then purifying

the material to obtain the desired isomer substantially free of other isomers), Applicant is reminded that this limitation is a process limitation (i.e., directed to a process of obtaining and/or preparing the compound) and, thus, fails to materially or structurally limit the claimed composition as a whole. Accordingly, since the cited reference(s) clearly renders obvious the same combination of the claimed components, the process Applicant intends to prepare the claimed isomer or composition thereof is immaterial to the composition as a whole. As directed by the MPEP at §2113, "Even though product-by-process claims are limited by and defined by the process, *determination of patentability is based on the product itself.* The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process" (see *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985 and MPEP §2113)).

Regarding (2), Remington's Pharmaceutical Sciences (p.420-425) teaches that drugs are formulated into salts to modify the duration of action of a drug; to modify the transportation and distribution of the drug in the body; to reduce toxicity; and to overcome difficulties encountered in pharmaceutical formulation procedures or in the dosage form itself (col.2, p.424, para.1).

One of ordinary skill in the art at the time of the present invention would have found it *prima facie* obvious to employ a salt formulation of the desired pharmacologically active isomers with the greatest activity of the N-cyanobenzylamphetamine compound (i.e., amphetaminil) as disclosed by Salvesen et al. because, as evidenced by Remington's, pharmaceutical salt formulations are known to modify the duration of action of a drug, modify the transportation and distribution of the drug in the body, reduce toxicity, and to overcome difficulties encountered in pharmaceutical formulation procedures or in the dosage form itself. Thus, it would have been *prima facie* obvious to the skilled artisan motivated by any one or more of these factors to formulate the desired pharmacologically active isomers with the greatest activity of the N-cyanobenzylamphetamine compound (i.e., amphetaminil) of Salvesen et al. into

a pharmaceutically acceptable salt to enhance the pharmacokinetic parameters of the drug or to reduce the toxicity with the reasonable expectation that the therapeutic benefit of the agent in salt form would have been the same or substantially similar to that of the parent amphetaminil compound itself.

Regarding (3), directed to the use of the pharmaceutical composition for the treatment or prevention of a disorder benefiting from or requiring a central nervous system stimulant (claim 30), such as, e.g., narcolepsy, attention deficit hyperactivity disorder, etc. (claim 31), though it is noted that the cited reference(s) may not explicitly teach such a use as instantly claimed, the limitations of present claims 30-31 directed to the use of the claimed composition for the treatment or prevention of a disorder benefiting from or requiring a central nervous system stimulant is an intended use of the composition (i.e., an intent to use the composition for the treatment or prevention of such a disorder), which does not impart any physical or material characteristics to the composition that are not already present in the composition suggested by the prior art. If the body of a claim fully and intrinsically sets forth all of the limitations of the claimed invention, and the preamble merely states, for example, the purpose or the intended use of the invention, rather than any distinct definition of any of the claimed invention's limitations, then the preamble of the claim is not considered a limitation and is of no significance to claim construction. See *Pitney Bowes, Inc. v. Hewlett-Packard Co.*., 182 F.2d 1298, 1305, 51 USPQ2d 1161, 1165 (Fed. Cir. 1999). See also *Rowe v. Dror*, 112 F.3d 473, 378, 42 USPQ2d 1550, 1554 and MPEP §2112.02(II). In the instant case, the cited prior art meets each and every structural and physical limitation of the instantly claimed pharmaceutical composition and, thus, would be reasonably expected to be capable of performing the intended use as instantly claimed, absent factual evidence to the contrary and further absent any apparent structural difference between the composition of the prior art and that of the instant claims.

Response to Applicant's Arguments

Applicant traverses the instant rejection, stating that Applicant has shown that the claimed isomeric configuration is more effective as a stimulant and has fewer movement-related side effects as compared to the racemate, which is an unexpected result. Applicant alleges this result was not predictable and asserts that the artisan would have expected the opposite effect, i.e., that a compound's toxicity would increase with its increased therapeutic effect. Still further, Applicant alleges that "the fact that the isolated stereoisomers are less stable than the racemate points to the unpredictability of characterizing the properties of stereoisomers based on the properties of the racemate."

Applicant's traversal has been fully and carefully considered, but fails to be persuasive.

Initially, it is noted that Salvesen et al. does, in fact, explicitly disclose that the two diastereoisomeric mixtures derived from racemic amphetaminil each have a general stimulant effect. Please see Salvesen et al., col.1, para.1, p.137. As evidenced by Salvesen et al., amphetaminil contains four stereoisomers that form two diastereoisomeric mixtures, the [(αS, α'R),(αS, α'S)] N-cyanobenzylamphetamine mixture derived from (S)-(+)-amphetamine and the [(αR, α'R),(αR, α'S)] N-cyanobenzylamphetamine derived from R-(-)-amphetamine.

The isolation of the single isomeric mixture, out of *two* possible identified isomeric mixtures, that has the greater biological activity was a procedure well within the technical skill of the one of ordinary skill in the art at the time of the invention who would have expected that the isomers would have differed in activity such that one isomer had greater biological activity that the other. This reasonable expectation of different biological activity results from the fact that living systems are chiral and, thus, preferentially process certain stereochemical configurations over others. As a result, optically active isomer isolation from a mixture, particularly when only two diastereoisomeric mixtures have been identified, would have been *prima facie* obvious to one of skill in the art at the time of the invention in view of (1) the reasonable expectation of greater activity from one isomeric configuration over the other, (2) the fact that the skilled

artisan would have had within his possession knowledge of conventional methods of purification (such as, e.g., various chromatographic methods), (3) the fact that the skilled artisan would have been motivated to isolate this single isomer or isomeric mixture with greater activity from the disclosed mixture due to the desire to produce a pharmaceutical composition that produces an optimal therapeutic effect and (4) the number of isomers (and isomeric mixtures) is finite and of a small magnitude (i.e., only four isomers and two isomeric mixtures) such that the use of known techniques to isolate and determine the activity of each isomeric mixture of such a small genus of identified isomeric configurations to determine the one with the greatest stimulant activity was well within the technical grasp of the skilled artisan familiar with the chemical, pharmaceutical and medicinal arts. Please reference *In re Anthony* (citation *supra*) and *In re Adamson*, 125 USPQ 233 (citation *supra*).

Accordingly, though Salvesen et al. may not explicitly disclose that the [(αR, α'R),(αR, α'S)] N-cyanobenzylamphetamine mixture has greater stimulant efficacy, Salvesen et al. clearly places each of the two isomeric mixtures within the possession of the artisan by explicitly teaching each of the two known isomeric mixtures and, therefore, the identification and isolation of the one isomeric mixture out of the two disclosed with the greater biological activity would have been a practice that would have been obvious to, and well within the skill, of the artisan imbued with (1) the reasonable expectation that one isomeric mixture of the two disclosed would have had greater activity and (2) a desire to produce an optimally effective therapeutic composition by purifying the mixture to contain the one isomeric mixture of greater biological activity.

Applicant's reliance upon the fact that the claimed isomeric mixture has greater stimulant activity with fewer movement-related side effects as compared to the racemate as evidence of an unexpected result has been fully and carefully considered, but fails to be probative of nonobviousness of the instantly claimed subject matter. It is agreed that the data and evidence presented in the specification demonstrates that (1) the claimed isomeric mixture functions more effectively as a stimulant than the other isomeric

mixture and (2) that claimed isomeric mixture has fewer movement-related side effects than the other isomeric mixture. However, the data fails to demonstrate that the results seen with this single isomeric mixture instantly claimed were *unexpectedly* greater than what would have already been *expected* by one of ordinary skill in the art at the time of the invention. Please see MPEP §716.02(b)[R-2], which states, "The evidence relied upon should establish 'that the differences in results are in fact unexpected and unobvious and of both statistical and practical significance.' *Ex parte Gelles*, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992)".

The fact that the skilled artisan *reasonably expects* that one of the isomeric mixtures of a finite number of isomeric mixtures and configurations (i.e., in this case, either two possible isomeric mixtures or four single isomers) will have greater biological activity than the other(s) due to the fact that living systems are chiral and, thus, preferentially process certain stereochemical configurations over others is clear evidence that this property of greater biological activity from one of the isomers is already recognized in the prior art. Therefore, this property of greater biological activity of the instantly claimed isomeric mixture is *not per se* unexpected, but rather is *comparable to what is already expected* from the prior art. The establishment of a property that is also found in the prior art fails to provide a patentable distinction between the products and, therefore, is insufficient to rebut the evidence of obviousness. Please see MPEP §716.02(c)[R-2] ("Where the unexpected properties of a claimed invention are not shown to have a significance equal to or greater than the expected properties, the evidence of unexpected properties may not be sufficient to rebut the evidence of obviousness. *In re Nolan*, 553 F.2d 1261, 1267, 193 USPQ 641, 645 (CCPA 1977).") In other words, though Applicant asserts that the allegedly unexpected effect(s) of the instantly claimed isomeric configuration was unpredictable from the disclosure of the prior art, it remains that the prior art acknowledges a clear expectation of differing biological activities of different isomeric configurations and that this expectation is, thus, predicted by the skilled artisan.

In view of the foregoing, and further in view of the fact that the evidence presented in the specification and relied upon in Applicant's remarks fails to present any evidence or discussion as to why the data contained therein demonstrates properties and/or characteristics of biological activity that are *not* expected by one of ordinary skill in the art at the time of the invention, the totality of rebuttal evidence of nonobviousness fails to outweigh the evidence in support of the instant conclusion of *prima facie* obviousness when all of the evidence and remarks are considered. Accordingly the rejection is properly maintained.

For these reasons, and those previously made of record at p.2-6 of the Office Action dated June 12, 2008, rejection of claims 1-8 and 28-31 is proper.

Conclusion

Rejection of claims 1-8 and 28-31 is proper.

Claims 25-27 are **withdrawn** from consideration pursuant to 37 C.F.R. 1.142(b).

No claims of the present application are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Leslie A. Royds/
Patent Examiner, Art Unit 1614

December 2, 2008

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614